WOUND HEALING: AN OVERVIEW

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Introduction

A wound is defined as damage or disruption to the normal anatomical structure and function.[1] As surgeries in the oral cavity include the soft and bony tissue it is essential to know their individual wound healing processes and the correct and efficient wound management.[2]

Soft tissue healing

Traditionally, wound healing has been divided into three distinct phases: inflammation, proliferation, and remodelling.[3,4] The first phase usually starts instantly after injury, then through day four to six.

The inflammatory phase consists of three main parts: haemostasis, chemotaxis, and increased vascular permeability. These will help in limiting further damage, closing the wound, removing cellular debris and bacteria, and fostering cellular migration.[5] The main cells involved in this phase are neutrophils, macrophages and lymphocytes.[6] The neutrophils enable phagocytosis of cellular debris and bacteria, therefore allow decontamination of the wound. Furthermore, they produce two different types of proteases: serine proteases and metalloproteinases.[3,4] Macrophages release cytokines that promote the inflammatory response and ultimately recruit and activate leukocytes.[7] Moreover, they induce and clear apoptotic cells and lay the foundation for the resolution of inflammation.[7] The lymphocytes play a regulatory role and increase wound maturation and the cross-linking of collagen.[3,4]

The proliferative phase contains the formation of granulation tissue, reepithelialisation, and neovascularisation and lasts from day four until day 14.[3,4,5]

Finally, the maturation and remodelling phase lasts from day eight up to one year. Clinically, this phase is perhaps the most important, as it involves contracting the wound mediated by myofibroblasts and collagen synthesis.[3,4,6]

Some authors divide wound healing into four stages instead of three, separating haemostasis and inflammation into two individual stages.

Bone healing

Bone healing can occur in two different ways – by primary or secondary intention. The latter being the important one in oral surgery, as extraction sockets heal by secondary intention.[8] Primary intention takes place when the bone is incompletely fractured or if the fractured ends are reapproximated closely and then stabilised rigidly.[9] If the bone ends are 1mm or more apart, the bone heals by secondary intention.[9] It can also be divided into three stages:

- The early inflammatory stage
- The repair stage
- The remodelling stage.[10]

The secondary intention or indirect bone healing is characterised by callus formation.[11] Its steps can be summarised as follows:

1. Inflammation and haematoma formation
2. Fragment stabilisation by periosteal and endosteal callus formation
3. Continuity restoration by membranous and endochondral bone formation

4. Formation of osteons and Haversian canals and functional adaption.[11]

Factors that affect wound healing in bone and soft tissue

Flap design

An injudicious flap design may interfere with wound healing. A slight trapezoidal shape of the flap with a wide base is favourable to ensure good blood perfusion.[12] Tissue trauma, due to stretching or tearing of the flap, as well as tension on the wound after suturing, must be avoided to prevent increased scar formation or delayed healing.[12]

Suture selection

A review of tissue reactions to different suture materials by Javed *et al* showed that monofilament materials had a significantly lower tissue reaction compared to multifilament materials.[13] They concluded that bacterial adherence to sutures is substantial in inducing tissue reactions and reviewed studies that discovered that the least number of bacteria can be found in nylon, whereas the adherence to silk is significantly higher. These findings class as level one on the hierarchy of evidence and are clinically relevant as they suggest that silk should not be used in surgeries in the oral cavity.

Local factors

Infection

Exodontia and dental surgery allow bacteria to contaminate and disturb deeper soft and bony tissues. As mentioned above, inflammation is part of wound healing. It is critical to the removal of contaminating micro-organisms. Studies show that giving the patient a pre-operative antimicrobial mouthwash reduces the number of bacteraemia cases[14] and the duration of post-extraction bacteraemia significantly.[15] In these studies the use of chlorhexidine mouthwash is recommended. The systematic review and meta-analysis by Arteagoitia *et al* and the randomised controlled clinical trial by Barbosa *et al* are both categorised as level one on the hierarchy of evidence.[14,15] They can therefore be seen as reliable and their findings should be applied to clinical practice. Additionally, the use of antibiotics is one of the most effective means to reduce the risk of wound infection,[16] but prescribing prophylactic antibiotics should be scrutinised critically as antimicrobial resistance in bacterial pathogens has become a significant challenge for clinicians.[17]

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Oxygenation

Oxygen plays a crucial role in wound healing, as it is important for cell metabolism.[7] Literature shows that it prevents wounds from infection, induces angiogenesis, increases keratinocyte differentiation, migration and re-epithelialisation, enhances fibroblast proliferation and collagen synthesis, and promotes wound contraction.[7,18,19] Early wounds are usually quite hypoxic, due to vascular disruption and high oxygen consumption by metabolically active cells. Therefore, healing will be compromised if the wound‘s oxygenation is not restored. These compromises can rise because of conditions such as advanced age or systemic diseases, for example diabetes. Here, we may find impaired blood flow and hence, poor tissue oxygenation.

Systemic factors

Age

It is well known that there are differences in wound healing between young and aged individuals and that an increased age is a major risk factor for impaired wound healing.[6,7] For one, ageing affects the inflammatory phase as it prolongs the production of inflammatory cytokines, which ultimately delays the healing and tissue fibrosis, therefore reducing regenerative potential.[20] Secondly, it decreases collagen synthesis, cell migration, proliferation, and differentiation in the phase of new tissue formation and increases production and activity of matrix metalloproteinases and apoptosis in the remodelling phase.[20]

Smoking

It is common knowledge that smoking has a negative effect not only on wound healing, but is also carcinogenic.[21,22] An impaired wound healing in smokers has been noticed in oral surgery as well as in the placement of dental implants. Patients who smoke post-operatively show a delay in wound healing and an increase in different complications, such as infection, wound rupture, flap necrosis, and more.[7]

For example, a study from Goldminz and Bennett reviewed 916 flaps and full-thickness grafts and found that current high-level smokers (at least one pack per day) had necrosis develop approximately three times more frequently than never smokers, low-level smokers (less than one pack per day), or former smokers.[23] A systematic review and meta-analysis by Sørensen found that postoperative healing complications were higher in smokers compared to non-smokers and in former smokers compared to patients who never smoked.[21]

Alcohol consumption

Alcohol metabolism leads to formation of acetaldehyde, reactive oxygen radicals, and other molecules that damage healthy tissue.[11] An exposure to alcohol can cause impaired wound healing by weakening the early inflammatory response, hindering wound closure, angiogenesis, and collagen production, and alternating the protease balance at the wound site in the remodelling phase, therefore resulting in a weaker extracellular matrix.[7,24] Clinically, patients will present with slower healing accompanied by a tendency to return with any mechanical force.

Diabetes

Diabetes mellitus can severely disrupt wound healing, due to multifactorial causes. Poorly controlled blood sugars result in cellular dysfunction that impedes all phases of wound healing.[24] Individuals with diabetes have insufficient perfusion or angiogenesis, which leads to hypoxia, thus amplifying early inflammatory responses and increasing the risk of complications, such as infection.[20] In addition, sorbitol, a toxic by-product

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of glucose metabolism, accumulates in the tissues and a decrease of collagen in granulation tissue as well as defects in collagen maturation are found.[3,4]

Stress

Stress has a great impact on human health. The pathophysiology of it results in the deregulation of the immune system which causes a substantial delay in wound healing.[7]

Obesity

Obese individuals frequently face wound complications. As a consequence of a relative hypoperfusion and ischaemia that appears in subcutaneous adipose tissue a higher rate of surgical site infection appears in obese patients.[7]

Nutrition

Malnutrition can play an important role in wound healing. For example, a deficiency in protein intake can lead to reduced collagen production, angiogenesis and fibroblast proliferation.[24] There are also a number of vitamins involved in wound healing. The most closely associated being vitamin A and C. The role of vitamin E is still being discussed. It has been shown to affect a variation of host immune functions and studies on animals suggested that vitamin E supplementation is advantageous for wound healing but this has not yet been confirmed in humans.[25] The review by Hobson showed similar concerns. The reviewed research was generally Level 2b evidence, which can be considered reasonable.[26] However, it mostly involved rodents, hence the findings should not be assumed true for all patients.

Radiotherapy and chemotherapy

Radiotherapy and chemotherapy both impair wound healing greatly. The radiation beam affects not only cancerous tissue, but also the surrounding tissues by destroying the DNA and preventing cell replication needed for tissue injury.[24] The main effects of chemotherapy include a delayed inflammatory phase, decreased fibrin deposition and collagen synthesis, and delayed wound contraction.[24]

Medication

There are various medications which may hinder wound healing, such as non-steroidal anti-inflammatory drugs (NSAIDs) or steroids. They can interfere with clot formation or platelet function, or inflammatory responses and cell proliferation.[7] Clinical manifestations may include ulcers, wound dehiscence, bone necrosis, fistulas, and antrum perforations.[11]

Conclusion

Wound healing is a complex and vital part of oral and implant surgery. There are various local and systemic factors that can compromise its process. It is crucial to ensure that the risk of impaired wound healing is reduced as much as possible. This can be achieved by critically assessing the patient when planning the surgery, but also by correctly managing them clinically.

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